Is Osteoarthritis an Acquired Channelopathy?
A Novel Basic-Science Approach

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Summary

• Background of Work
• Basic Assumptions
• Important Discoveries
• Plans for Osteoarthritis Studies
Background

1996  Marino & LSU Co-workers
2000  Waddell and OSR Co-workers
2002  Genzyme Biosurgical Contract Support
Basic Assumptions
1 - Importance of Synovium

Type A: Macrophage  Type B: Secretory  M: Mast cell
Basic Assumptions
2 - Importance of Electrophysiology

Nystatin Patch Clamp
Experimental Approach

**Hypothesis**
Cell Electrical Changes → Function

**Methodology**
- Electrophysiology
- Enzyme Activity
- Molecular Biology → Composition
- Microscopy → Structure

**Objects of Study**
- HIG-82 Synovial Cells
- Synovial Biopsies
Important Discoveries

1. Signal Transduction in Synovial Cells

Early Events (15 minutes)

- $Ca^{2+}$
- $Na^+$
- $PKC$
- IL-1β receptor
- Voltage-gated $Ca^{2+}$ channel
- PKC-gated $Na^+$ channel

Synovial Cell
Important Discovery
Gap Junctions
Surgical Biopsy Procedure

20 mg
0.12 cm²
Important Discoveries

2. Gap Junctions Occur in Normal Human Synovium
Metalloproteinase (MMP) Assay
Important Discoveries

3. Gap Junctions are Essential for Synovial-Cell Secretory Response by Synovial Explants

![Graph showing MMP (mg/h/m²) with bars for C, IL-1, +GR, +Oct. * P < 0.05, N=4]
Modified Model

- **IL-1β**
- **IL-1β receptor**
- **PKC-gated Na⁺ channel**
- **PKC**
- **Ca²⁺**
- **Na⁺ (Vm↓)**
- **Voltage-gated Ca²⁺ channel**
- **Gap-junction channel**
- **Relative Ca²⁺ concentration**
- **MMPs**

Diagram shows the interaction of these components with arrows indicating direction and intensity of the effects.
Important Discoveries
4. Relation Between Gap Junctions and Osteoarthritis

• Larger number of gap junctions in OA
• More gap-junction protein in OA (connexin 43)
• Larger gap junctions in OA
Important Discoveries
5. Synovial Cells Undergo a Phenotypic Change During the Development of Osteoarthritis

MMP Production by Synovial Tissue

MMP (mg/h/m²)

Control Patients  |  OA Patients

No IL-1β  |  IL-1β

MMP Production by Synovial Tissue
Important Discoveries
6. Hyaluronan Antagonizes MMP Production: The Effect is Concentration- and Size-Dependent

Effect of Hyalgan and Synvisc on IL-1β Induced MMP Activity from Synovial Tissue of Osteoarthritis Patients
Present Status of Osteoarthritis Research

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* Requesting 600K over 5 years from NIH
Profound Electrical Changes Occur in Synovial Cells Within Minutes of Exposure to Inflammatory Cytokines

Effect of Cytokines on Current-Voltage Curves in HIG-82 Synovial Cells
Proposed Membrane-Channel Research

Basic Idea \[\Rightarrow\] Pathological changes in specific synovial-membrane ion channels mediate progression of OA

Proposal \[\Rightarrow\]

1) Identify the channels functionally by comparing OA and normal synovial cells

2) Design agents to activate/inhibit the altered function to arrest or release the disease